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Loss of SMARCA4 Expression is both Sensitive and Specific for the Diagnosis of Small Cell Carcinoma of Ovary, Hypercalcemic Type

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Abstract

Small cell carcinoma of ovary, hypercalcemic type (SCCOHT) is a rare ovarian neoplasm that occurs in young women and has a poor prognosis. The histologic diagnosis of SCCOHT can be challenging due to its rarity and relatively non-specific histologic features, which range from the classic, first-described small cell morphology to a pattern in which there are large cells with abundant eosinophilic cytoplasm. Many entities can be in the differential diagnosis and to date, immunohistochemical stains have shown no distinctive profile and have been of limited aid. *SMARCA4* (also known as *BRG1*) mutations have recently been reported at high frequency in these tumors. *SMARCA4* is an important component of the SWI/SNF complex which regulates gene expression through alteration of nucleosome conformation. Studies to date have suggested that immunohistochemical loss of expression of *SMARCA4* is associated with the presence of a *SMARCA4* mutation in most cases. In this study, the sensitivity and specificity of the immunohistochemical loss of *SMARCA4* expression for the diagnosis of SCCOHT is examined in the context of the differential diagnosis with other primary or metastatic ovarian tumors. All but one of the SCCOHT showed loss of *SMARCA4* expression (16/17; 94%), while of 279 other tumors tested, only two tumors (one clear cell carcinoma and one ovarian melanoma) showed loss of *SMARCA4* expression. We conclude that *SMARCA4* immunohistochemistry is highly sensitive and specific for a diagnosis of SCCOHT and is of clinical utility in the differential diagnosis of poorly differentiated ovarian tumors.

INTRODUCTION

Small cell carcinoma of the ovary, hypercalcemic type (SCCOHT) is a rare, poorly-differentiated ovarian malignancy of uncertain lineage which presents in young women and is associated with poor clinical outcome and, in many cases, hypercalcemia.¹ Histologically, the tumor is usually composed of small, hyperchromatic, mitotically-active cells with follicle-like spaces, although up to 40% of cases demonstrate areas of large cell

morphology.^{1, 2} Several recent studies have reported a high frequency of inactivating, predominantly nonsense, splice-site or frameshift *SMARCA4* (also known as *BRG1*) mutations in these tumors, which lead to loss of protein expression.³⁻⁶ No other recurrent mutations were detected in SCCOHT in these studies.⁴

SMARCA4 acts as a catalytic ATPase subunit in the Switch/Sucrose Non Fermentable (SWI/SNF) complex, which regulates gene expression by remodeling chromatin to alter nucleosome conformation.⁷ In non-neoplastic cells, this complex acts to regulate the specific gene expression programs in different cell types,⁷ while in vitro studies on neoplastic cells have suggested a role for the SWI/SNF complex in the regulation of expression of both oncogenes and tumor suppressor genes.⁸ Other key subunits of SWI/SNF include *SMARCB1*, *ARID1A* and *ARID1B*. It is estimated that mutations in SWI/SNF components occur in up to 20% of tumors, with mutations in *SMARCA4* being among the most common.⁹ *SMARCA4* mutations (predominantly missense) have been previously reported in carcinomas of multiple sites, including lung^{10,11} and pancreas¹² and even in ovarian epithelial neoplasia¹³ and endometrial carcinoma.¹⁴ However, the significance of the *SMARCA4* mutation in the process of tumorigenesis in these complex, genetically unstable carcinomas is unclear. In contrast, as the only recurrent mutation demonstrated in SCCOHT to date,⁴ *SMARCA4* mutation appears likely to be a major driver in SCCOHT tumorigenesis.

Immunohistochemical studies on *SMARCA4* expression have demonstrated loss of expression in the vast majority of SCCOHT with confirmed *SMARCA4* mutations, suggesting that the presence of *SMARCA4* mutation can be inferred using immunohistochemistry.^{3, 4} In addition, Ramos et al⁴ performed immunohistochemistry on a range of primary ovarian epithelial, sex cord stromal and germ cell tumors and demonstrated that only 2 of 485 tumors showed loss of expression of *SMARCA4*. Both tumors with loss of *SMARCA4* expression were ovarian clear cell carcinomas. These initial results suggested that in the differential diagnosis of primary ovarian tumors, loss of *SMARCA4* expression is both sensitive and specific for SCCOHT. However, the data available on *SMARCA4* expression in rare tumors such as small cell carcinoma of ovary, pulmonary type (SCCO-PT) and granulosa cell tumor, juvenile-type (GCT-J) is currently very limited, due to the low numbers of tumors tested to date. Prior immunohistochemical studies have focused exclusively on the pattern of *SMARCA4* expression of primary ovarian tumors. However, the ovary is a frequent site of metastasis and the differential diagnosis between a SCCOHT and various metastatic tumors can represent a diagnostic challenge.

In this study, we investigated *SMARCA4* immunohistochemical expression in a range of tumors which may secondarily involve the ovary. Furthermore, we aimed to expand our knowledge of the *SMARCA4* expression profiles of primary ovarian tumors, some of which may feature in the differential diagnosis of SCCOHT, by studying cohorts of both common ovarian epithelial tumors and rarer ovarian tumor types, including sex cord stromal tumors.

METHODS

Case Selection

Having secured institutional research board (IRB) approval, 17 SCCOHT were identified from the pathology database of the participating institutions, including the personal consult files of three expert gynecologic pathologists (RAS, EO, RHY). Other primary ovarian tumors in the differential diagnosis of SCCOHT were identified from the pathology database at Memorial Sloan Kettering Cancer Center (MSKCC), including epithelial tumors (small cell carcinoma, pulmonary type (SCCO-PT)[n=2], clear cell carcinoma (CCC) [n=37], endometrioid carcinoma (OEC) [n=38], high-grade serous carcinoma (HGSC) [n=42]), and sex cord stromal tumors (SCST) (including granulosa cell tumor, adult-type (GCT-A) [n=42], granulosa cell tumor, juvenile-type (GCT-J) [n=11], Sertoli Leydig cell tumor (SLCT) [n=6], gynandroblastoma (GAB) [n=2] and sex cord stromal tumor not otherwise specified (SCST NOS) [n=3]). Non-ovarian tumors tested included lung small cell carcinoma (LSCC) [n=26], small cell carcinoma of uterine cervix (CSCC) [n=2] or corpus (USCC) [n=1], gynecologic tract melanoma [n=31] and desmoplastic small round cell tumor (DSRCT) [n=36]. Seven of the lung SCCs tested were from a metastatic site (liver), while 18 were from the primary lung lesion. Of the three melanomas involving the ovary, one was of unknown primary site, while the remaining two were metastases from primary skin melanomas. The remaining melanomas tested involved the vulva [n=14], vagina [n=12] and cervix [n=2].

Immunohistochemistry

One whole formalin-fixed, paraffin-embedded section of tumor from each case was evaluated using a murine monoclonal SMARCA4 antibody raised against amino acids 209–296, mapping near the N-terminus of SMARCA4 of human origin (Clone G-7, Santa Cruz Biotechnology, Texas, USA). All staining procedures were performed on a Leica Bond-RX (Leica, Buffalo Grove, IL) automated stainer platform. For the immunohistochemical detection of brg1, mAb G-7 (SC17796; Santa Cruz Biotechnology, Dallas, TX) was used at a dilution of 1:500 (0.4 µg/ml). Primary incubation time was 30 minutes. Heat-based antigen retrieval was employed using an EDTA-based retrieval buffer (ER2, Leica) for 30 minutes. As secondary reagent, a polymer detection kit (Refine, Leica) was used. In tumors with loss of SMARCA4 protein expression, positive staining of endothelial cells and stromal cells was used as an internal positive control. A tumor was adjudged to demonstrate loss of expression when all tumor cells were negative for SMARCA4 immunostaining, in the presence of a positive internal control. Reduced, focal or attenuated tumor positivity was counted as retention of protein expression. Non-SCCOHT tumors with highly attenuated or negative SMARCA4 staining underwent repeat staining using the same technique for confirmation of the initial result.

RESULTS

The results of SMARCA4 immunohistochemistry are presented in Table 1. Sixteen of seventeen SCCOHT tested (94%) demonstrated complete loss of expression of SMARCA4 (Figure 1). The presence of an in-frame deletion leading to the production of a truncated,

non-functional protein had previously been reported in the single SCCOHT with retained SMARCA4 expression.⁴ Among all ovarian carcinoma subtypes tested, only one CCC showed complete loss of SMARCA4 expression (1/37; 3%) (Figure 2). The SMARCA4-negative CCC was a Stage IV, widely disseminated tumor with both clear and oxyphilic morphology, and papillary and tubulocystic architecture. The tumor occurred in a 49 year old woman who died from disease within one year of diagnosis, despite treatment with multiple lines of chemotherapy. All ovarian SCSTs tested showed uniform positive SMARCA4 staining, including GCT-A, GCT-J, SLCT and GAB (Figure 3). All SCCO-PT, HGSC, and OEC tested showed retained SMARCA4 expression (Figure 4).

One of thirty one melanomas tested showed complete loss of SMARCA4 expression (3%), an ovarian melanoma with no other known primary site. Histologically the tumor did not morphologically resemble SCCOHT, being composed of cells with abundant cytoplasm, small round nuclei and prominent melanotic pigment (Figure 5). All lung SCC, gynecologic tract SCC, and DSRCTs tested showed strong retained expression of SMARCA4 (Figure 6).

Thus, in the cohort studied, loss of SMARCA4 expression had a sensitivity of 94% and a specificity of 99.3% for the diagnosis of SCCOHT.

DISCUSSION

In this immunohistochemical study of a range of primary ovarian and non-ovarian tumors, we have demonstrated that loss of SMARCA4 expression is both sensitive and specific for the diagnosis of SCCOHT, and thus is of clinical utility in the differential diagnosis of a wide range of poorly differentiated tumors involving the ovary. The spectrum of small cell and large cell phenotypes that may be encountered in SCCOHT result in many tumors potentially being in the differential diagnosis¹⁵ and no immunohistochemical findings had previously been shown to be discriminative for the diagnosis of SCCOHT.

The classic morphologic appearance of SCCOHT involves sheets of small, uniform, mitotically-active cells with variously conspicuous follicle-like spaces. In up to 40% of tumors however, a component of larger, more pleomorphic and sometimes rhabdoid-like cells can be seen.^{1, 2, 16} When these large cell areas predominate, the tumor is referred to as "SCCOHT, large cell variant".¹ Immunohistochemical studies have described a non-specific profile of variably-intense positive staining for EMA, pan-keratin, WT1 and CD10 and negativity for α -inhibin and TTF-1.² Variable immunohistochemical staining for neuroendocrine markers has been reported, with positivity for chromogranin or synaptophysin identified in a minority of cases.^{1,2} While the diagnosis of SCCOHT can be made on morphological grounds in most cases if the observer has experience with the entity, most pathologists who first encounter this neoplasm will have seen no prior examples. Furthermore, even those who have seen one or more examples can have diagnostic difficulties as rare primary ovarian epithelial tumors such as SCCO-PT or malignant sex cord tumors not otherwise specified (NOS) can histologically resemble SCCOHT. Additionally, poorly differentiated tumors in the sex cord group, which often occur in the young, can demonstrate a non-specific morphologic and immunohistochemical profile, with attenuated staining for traditional markers of sex cord stromal differentiation such as

calretinin and inhibin. Our study confirms the initial findings of Ramos et al⁵ and Karanian-Phillips that SMARCA4 immunohistochemistry can help in the differential diagnosis between these tumors and SCCOHT. This paper also highlights a rare diagnostic pitfall which can occur with the use of SMARCA4 immunohistochemistry in SCCOHT, where there is retention of protein expression despite the presence of a *SMARCA4* in-frame deletion (previously demonstrated in the single SMARCA4-positive SCCOHT by Jelinic et al)⁴. Thus, SMARCA4 immunohistochemical results should be interpreted in the context of the clinical scenario and morphologic features, and further testing, such as sequencing analysis can be undertaken when diagnostic uncertainty remains.

Another recent paper reports loss of SMARCA4 expression in un- and de-differentiated endometrial carcinomas.¹⁸ As the undifferentiated component of de-differentiated carcinomas showed preferential loss of SMARCA4 expression, it was hypothesized that SWI/SNF alterations may play a role in the progression and/or de-differentiation of certain endometrioid carcinomas of endometrium. Undifferentiated and de-differentiated carcinomas of ovary are extremely uncommon tumors,^{19,20} but do show some morphologic similarity to SCCOHT. In particular, the large cell variant of SCCOHT may be histologically similar to rhabdoid tumor cells that are sometimes found in un- and de-differentiated carcinomas. Since the median age of patients with un- and de-differentiated carcinomas is 51–59 years,^{19,20,21} most cases should be distinguishable by virtue of the patient's age, although this is not a highly specific data point. Any differentiated endometrioid carcinomatous component would support a diagnosis of de-differentiated carcinoma. Our own anecdotal experience also indicates that cytokeratin and EMA expression tends to be much more diffusely distributed in SCCOHT than in un- and de-differentiated carcinomas. Last, the role that SMARCA4 plays in each tumor type appears to be different, with SMARCA4 germline mutation being common in SCCOHT^{4,5,6,22,23,24} and acquired SMARCA4 mutations being more common in un- and de-differentiated carcinomas, particularly in the setting of defective DNA mismatch repair.¹⁸

There can also be extensive morphologic and immunohistochemical overlap between metastatic tumors to the ovary and SCCOHT. SMARCA4 immunohistochemistry represents a further diagnostic tool in the differential diagnosis between metastatic small cell carcinoma involving the ovary and SCCOHT, adding to the current approach which utilizes a combination of clinicoradiologic correlation, careful tumor sampling to detect a minor differentiated component (for example, with mucinous or endometrioid features) and assessment of additional informative primary site-specific parameters such as evidence of Human Papilloma Virus (HPV) infection in metastatic cervical tumors.^{25,26} In young patients, desmoplastic small round cell tumor can be an important differential diagnosis of SCCOHT. While DSRCT is considered to have a characteristic immunohistochemical profile and intraabdominal pattern of widespread serosal involvement, SMARCA4 immunohistochemistry can be helpful in ruling out a SCCOHT with extensive intraperitoneal dissemination.²⁷

In common with the results of Ramos et al,⁵ we found that rare ovarian clear cell carcinomas (CCC) demonstrate loss of SMARCA4 expression. This finding is intriguing in light of the high prevalence of mutations in *ARID1A* (another key component of the SWI/SNF

complex) in ovarian CCC (approximately 50%).^{28,29} However, it should be noted that *ARID1A* mutations also occur in up to one third of ovarian endometrioid adenocarcinomas,²⁹ which consistently show retention of SMARCA4 expression.⁵ Additionally, it is provocative to reflect on the fact that CCC is the second most common ovarian tumor associated with paraneoplastic hypercalcemia.³⁰ The only other tumor in our study cohort with loss of SMARCA4 expression was a melanoma which involved the ovary and was of uncertain primary origin. As SMARCA4 mutations have been reported in up to 10% of melanomas,⁹ this result was not unexpected, but highlights a potential diagnostic pitfall. However, a wider range of immunohistochemical markers, including melanocytic markers such as SOX10, S100, MelanA and HMB45 should facilitate accurate pathologic diagnosis.

The histogenesis of SCCOHT and where it falls precisely in the categorization of ovarian tumors has not been established to date. Dr. Robert E Scully, who first described this entity, placed it in the miscellaneous category of tumors.³¹ While features such as patient age distribution, immunohistochemical positivity for calretinin and frequent presence of follicle-like spaces within the tumor have been previously proposed as evidence for a sex cord lineage, other features such as negative α -inhibin and positive EMA immunohistochemistry argue against a sex cord origin.² Witkowski et al¹⁶ noted focal rhabdoid morphology in the large cell areas of SCCOHT and postulated that there may be a developmental link between extracranial atypical teratoid/rhabdoid tumors (AT/RTs) and SCCOHT, in light of the fact that a *SMARCA4* mutation-associated familial rhabdoid tumor predisposition syndrome has been described in recent years.^{32,33} The majority of familial rhabdoid tumors are associated with the presence of a germline *SMARCB1* mutation,^{34,35} another key component of the SWI/SNF complex. Foulkes et al³⁶ have suggested that SCHOTT should be renamed “malignant rhabdoid tumor of ovary (MRTO)” in light of these observations and longstanding issues with the nomenclature used in SCCOHT, including both the use of terminology such as “large cell variant of small cell carcinoma, hypercalcemic subtype”, which some find confusing, and the fact that SCCOHT may be associated with normal serum calcium levels. However, in light of the fact that this entity has been called “small cell carcinoma of ovary, hypercalcemic type” for almost 40 years,³¹ has accumulated an extensive body of literature over that time and is widely recognized under this name, we think that the proposal to change the current nomenclature is premature. Furthermore, while SCCOHT can in some cases demonstrate the presence of rhabdoid cells (a feature in common with rhabdoid tumors), the majority do not, a fact that makes it inappropriate to consider them synonymous. Rather than exchanging one inexact, histology-based label with another, it is preferable to await further developments in the field of molecular pathology to establish what nomenclature is best for this tumor. In the future, it may be considered appropriate to create a “SMARCA-gene mutated” tumor category involving multiple sites, which is principally defined not by histologic features but by the presence of such mutations. At this time however, we favor retention of the current, well-established term.

In summary, the loss of expression of SMARCA4 on immunohistochemistry can be considered highly sensitive and specific for the diagnosis of SCCOHT. SMARCA4

immunohistochemistry can be used both in the differential diagnosis of poorly differentiated primary ovarian tumors and to differentiate metastatic tumors from SCCOHT.

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Figure 1. Small cell carcinoma of ovary hypercalcemic type (SCCOHT)
SCCOHT (large cell variant) H&E (A) and negative SMARCA4 IHC in tumor with stroma providing the positive internal control (B); SCCOHT H&E (C) and negative SMARCA4 IHC (D)

Figure 2. Clear cell carcinoma of ovary

Clear cell carcinoma H&E (A) and negative SMARCA4 IHC (B); Clear cell carcinoma H&E (C) and positive SMARCA4 IHC (D)

Figure 3. Sex cord stromal tumors

Granulosa cell tumor, adult-type (A) and positive SMARCA4 IHC (inset); Granulosa cell tumor, juvenile type H&E (B) and positive SMARCA4 IHC (inset); Sertoli-Leydig cell tumor H&E (C) and positive SMARCA4 IHC (inset); granulosa-cell-like component of a gynandroblastoma H&E (D) and positive SMARCA4 IHC (inset)

Figure 4. Ovarian epithelial tumors

Ovarian endometrioid carcinoma H&E (A) and positive SMARCA4 IHC (inset); High-grade serous carcinoma H&E (B) and positive SMARCA4 IHC (inset); Ovarian small cell carcinoma, pulmonary-type H&E (C) and positive SMARCA4 IHC (inset); Small cell component of an ovarian carcinosarcoma H&E (D) and positive SMARCA4 IHC (inset)

Figure 5. Melanoma in ovary

Ovarian melanoma H&E (A) and negative SMARCA4 (B); Ovarian melanoma H&E (C) and positive SMARCA4 IHC (D)

Figure 6. Tumors that may metastasize to the ovary

Pulmonary small cell carcinoma H&E (A and B) and positive SMARCA4 IHCs (insets);
Cervical small cell carcinoma H&E (C) and positive SMARCA4 IHC (inset); Desmoplastic
small round cell tumor H&E (D) and positive SMARCA4 IHC (inset)

Table 1

TUMOR TYPE	N	LOSS OF SMARCA4 EXPRESSION
SCCOHT	17	16/17 (94%)
OVARIAN EPITHELIAL TUMORS		
Ovarian SCC, Non-SCCOHT-type	2	0/2 (0%)
Ovarian CCC	37	1/37 (3%)
Ovarian EC	38	0/38 (0%)
Ovarian HGSC	42	0/42 (0%)
OVARIAN SEX CORD STROMAL TUMORS (SCST)		
Ovarian GCT, Adult-type	42	0/42 (0%)
Ovarian GCT, Juvenile-type	11	0/11 (0%)
Ovarian SLCT	6	0/6 (0%)
Ovarian GAB	2	0/2 (0%)
Ovarian SCST NOS	3	0/3(0%)
METASTATIC MIMICS OF SCCOHT		
SCC, Lung	26	0/26 (0%)
SCC, Uterus/Cervix	3	0/3 (0%)
DSRCT	36	0/36 (0%)
Melanoma	31	1/31 (3%)

SCCOHT small cell carcinoma of hypercalcemic types, SCC small cell carcinoma, CCC clear cell carcinoma, EC endometrioid carcinoma, HGSC high grade serous carcinoma, SCST sex cord stromal tumors, GCT granulosa cell tumor, SLCT Sertoli Leydig cell Tumor, GAB gynandroblastoma, NOS not otherwise specified, DSRCT desmoplastic small round cell tumor.